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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/723,722	11/28/2000	John P. Anderson	00228-US-NEW2C1	9856

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EXAMINER

WALICKA, MALGORZATA A

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 12/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/723,722

Applicant(s)

ANDERSON ET AL.

Examiner

Malgorzata A. Walicka

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 November 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-13, 15, 18, 19, 22-25, 27-37, 39-53, 132 and 133 is/are pending in the application.
- 4a) Of the above claim(s) 5-13, 19, 27, 28, 37 and 39-53 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 15, 18, 22-25, 29-36, 132 and 133 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 12/09/02 & 11/22/04
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: sequece alignment.

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A request for continued examination under 37 CFR 1.114, including Information Disclosure Statement and the fee set forth in 37 CFR 1.17(e), was filed in this application Nov. 22, 2004, after advisory action. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114.

Claims 1-13, 15, 18-19, 22-25, 27-37, and 39-53 and 132-133 are pending in the application. Claims 1-4, 15, 18, 22-25, 29-36 and 132-133 are the subject of this Office Action; claims 5-13, 19, 27-28, 37 and 39-53 stand withdrawn from further consideration.

Detailed Action

1. Rejections

1.1. 35 USC section 112, second paragraph

Claim 18 is reciting a confusing phrases "with respect to SEQ ID NO: 2" which renders the claim confusing. For examination purposes it is assumed that Applicants intention is to claim a protein whose N-terminal amino acid residue is 46, 58 or 63 and a C-terminus amino acid residue is between positions 452-501 of SEQ ID NO: 2.

Claim 15, 33 and 34 are directed to proteins or peptides having certain sequences. Because the specification does not teach whether open or closed claim language is intended, for examination purposes the transitional phrase "having" has the

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same meaning as comprising. i.e., the term "having" still permits inclusion of other moieties. See MPEP2111.03, **Other Transitional Phrases**.

Claim 32 is rejected because of the phrase "a peptide having fewer than about 15 amino acids". The double limitation "fewer than about" is indefinite. The peptide consists of 15 amino acids or fewer than 15 amino acids.

Claims 32 and 33 are confusing as directed to a composition comprising a beta-secretase inhibitor

- 1) comprising SEQ ID NO: 78, including conservative substitution thereof, and
- 2) comprising SEQ ID NO: 72, including conservative substitution thereof.

The language "comprising SEQ ID NO:78" or "comprising SEQ ID NO:72" does not allow any changes in SEQ ID NO:78 or 72, so "including conservative substitution" is unclear.

For examination purposes it is assumed that the language of claims is comprising sequence SEQ ID NO: 78 and comprising SEQ ID NO: 72.

1.1. 35 USC section 112, first paragraph

1.1.1. Lack of written description

Claim 1 and dependent claims 2-4, 22, 23, 24, 29-36, and 132-133 remain rejected under 35 U.S.C. 112 for lack of written description of structure or/and function, for reasons stated in the Final Office Action of February 20, 2004 and earlier Office Actions.

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The claims are directed to any protein purified to apparent homogeneity comprising a segment of any SEQ ID NO:2, wherein the segment lacks the signal sequence (amino acids residues 1-22 of SEQ ID NO: 2) and the putative proregion (amino acid residues 23-45 of SEQ ID NO: 2). Thus, the claims are directed to a large and variable genus of proteins for which there is no sufficient written description of the structure and function.

The scope of the claims encompasses proteins comprising fragments of SEQ ID NO:2 lacking amino acid residues 1-45 and consisting of at least amino acids 46-130 of SEQ ID NO:2. There is insufficient description of the structure and function of the genus of proteins towards which the claims are directed.

Claims 1, 3-4 22, 23 and 24 do not state the function of the claimed genus of proteins. Examiner understands that the desired function is that of beta-secretase. The specification discloses several species of said genus, i.e. proteins identified by SEQ ID NOs: 43, 58, 67, 68, 69, 70, 71, 75 for which the structure and function are known. These species, however, cannot identify the whole genus of the claimed proteins because said genus comprises proteins that do not have a beta-secretase activity or may have other enzymatic activity or no activity at all. For example, if a protein comprises a fragment of beta-secretase of SEQ ID NO: 2 consisting of amino acid residues 46-130, it is doubtful that the protein will have the enzymatic activity of a beta-secretase. Although the disclosure teaches that the fragment of beta-secretase of SEQ ID NO: 2 consisting of amino acids 63-419 has the desired enzymatic activity, there is nothing to suggest that shorter fragments do possess said activity especially when

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flanked by other amino acid sequences whose structure is not disclosed by Applicants. In conclusion, because lack of sufficient description of structure and function of the claimed proteins one skilled in the art is not reasonably convinced that that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Traversing the rejection for lack of written description, in their Remarks/Arguments filed August 19, 2004, Applicants write on page 25 third paragraph,

"Applicants respectfully submit Claim 1, as amended, complies with the written description requirement. Amended Claim 1 sets forth the structure of the claimed purified protein as a segment of SEQ ID NO: 2, the segment comprising valine at a position corresponding to position 130 of SEQ ID NO:2. Further, as acknowledged by the Examiner, the specification discloses numerous species of the recited β -secretase for which the structure is known, including SEQ ID NOS:43, 58, 67, 68, 69, 70, 71 and 75. Based on this disclosure, Applicants submit the specification provides sufficient description of the structure of the recited purified protein.

Applicants further submit the specification describes the structure/function relationship of proteins comprising the recited segments of SEQ ID NO:2. Figures 5a-5e describe relationship between the primary sequence and

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functional regions of SEQ ID NO:2. Further, the specification describes active forms of β -secretase (see at pages 30-32). In addition, the specification describes other functions of the recited β -secretase segments, such as, for example, the use of certain immunogenic fragments or oligopeptides of SEQ ID NO:2 in screening therapeutic compounds in a variety of drug screening assays (see Specification, page 50, line 14 to page 51, line 21.)"

Applicants' arguments have been fully considered but are found not persuasive for the following reasons:

- 1) **Claim 1 does not set forth the structure of the claimed purified protein as a segment of SEQ ID NO: 2 comprising valine at a position corresponding to position 130 of SEQ ID NO:2.** The claim is directed to a protein whose structure is set forth as comprising a segment of a beta-secretase enzyme protein comprising SEQ ID NO:2, the segment comprising valine at a position corresponding to position 130 of SEQ ID NO:2, wherein the segment lacks a signal sequence (amino acid residues 1-21 of SEQ ID NO:2 and the putative pro region (amino acid residues 22-45 of SEQ ID NO:2).
- 2) Claims 1-4, 22-24, 29-36, 132 and 133 are not limited to the numerous species for which the structure is known, including SEQ ID NOS: 43, 58, 67, 68, 69, 70,

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71 and 75 or species mentioned on pages 30-31 which refer to human brain species of recombinantly produced species.

- 3) Although the specification describes other functions of the recited β -secretase segments, such as, for example, the use of certain immunogenic fragments or oligopeptides of SEQ ID NO: 2 in screening therapeutic compounds in a variety of drug screening assays, the rejected claims are not directed to such other functions.

In addition to the above rejection, claims 32, 33 and 34 are rejected for lack of written description of beta-secretase inhibitors to be used in crystalline compositions. The claims are directed to compositions comprising three genera of inhibitors:

- 1) peptides fewer than 15 amino acids and comprising SEQ ID NO:78,
- 2) inhibitors comprising SEQ ID NO:72, and
- 3) inhibitors comprising SEQ ID NO:81.

The specification teaches peptides of SEQ ID NO: 78, 72 and 81, but providing these representative species for each of the claimed genus does not provide an identifying structural characteristics of each genus as a whole. Because of lack of written description of structure of the inhibitors of beta-secretase to be used in the claimed compositions one skilled in the art is not convinced that Applicants were in position of the claimed invention when the application was filed.

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1.1.2. Scope of enablement

Claim 1-4, 22, 23, 24, 29-36, and 132-133 remain rejected under 35 U.S.C. 112, first paragraph, for reasons stated in the Final Office Action.

In their response Applicants argue, "the specification further describes an assay for determining whether a segment of beta-secretase is active [thus enabling the claims]", page 27 of 30, line 3. Applicants' argument has been fully considered but is found not persuasive. Although the specification enables determining whether a segment of beta- secretase is active, the claims are not limited to active segments of SEQ ID NO: 2 or to a protein comprising such segments and having the function of beta- secretase.

1.2. 35 USC section 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting

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directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claim 1, 15, 22, 132-133 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 6,420,534, issued to Gurney et al., with priority to the provisional application 60/101,594 filed Sept. 24, 1998. The patent discloses human beta-secretase of SEQ ID NO:4, which is identical to SEQ ID NO:2 of the instant application. Thus SEQ ID NO:4 of Gurney et al.'s possesses all characteristic of the protein claimed in claim 1 of the instant application; see sequence alignment of the elected SEQ ID NO:43. As to claim 15, the term "having the amino acid sequence" has the meaning "comprising". Thus limitations of SEQ ID NO:15 read on characteristics of SEQ ID NO:4 of the patent.

The patent, see Examples 9, 10 and 11 discloses production of human beta-secretase of SEQ ID NO: 4, i.e. that of claim 1 of the instant invention, in heterologous cell of *E. coli*, insects and mammals.

1.3. 35 USC section 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject

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matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 23-25, 29-30 and are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,420,534, issued to Gurney et al., with priority to the provisional application 60/101,594 filed Sept. 24, 1998, in view of the common knowledge in molecular biology and US Patent No. 6,319,689, issued to Powell et al on Nov. 20, 2001, with priority date Jan. 28, 1997.

Claims 23-25 and 29-30 are directed to a crystalline protein composition of protein comprising a segment of SEQ ID NO:2 wherein said segment has valine in position 130 of SEQ ID NO:2 and lacks a signal sequence and putative pro-region, i.e., residues 1-45 of SEQ ID NO:2, wherein said protein

- (1) is purified to apparent homogeneity;
- (2) is non-glycosylated or glycosylated,
- (3) is in crystalline form with or without an inhibitor whose affinity is at least 1/100 of that exhibited toward SEQ ID NO:43, and
- (4) comprises SEQ ID NO:43.

Regarding point (1), the fact that β -secretase is purified to the apparent homogeneity is not a characteristic feature of the enzyme as such, unless the inventors disclose a new method specifically directed to purification of β -secretase, this, however,

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is not the case. The patent teaches methods of purification of isolated beta secretase in column 22, line 62 through column 23 line 18.

With respect to point (2) the fact that the protein is glycosylated or non glycosylated is not a characteristic feature of the enzyme as such, unless the inventors disclose a new method specifically directed to glycosylation or deglycosylation of the protein, this, however, is not the case. The protein in both forms is produced in the cell expressing the protein. Nonglycosylated forms are produced in prokaryotic host cells and glycosylated in eukaryotic host cells. Both forms of protein having characteristics of protein of claim 1 are taught by the patent, see column 22, line 52.

Regarding point (4), the patent does disclose the protein human beta-secretase having of 501 amino acids set forth by SEQ ID NO: 4 which is identical to SEQ ID NO: 2 of the instant application thus it comprises SEQ ID NO:43 and reads on structural limitations of the rejected claims.

Regarding point (3), the patent, however, does not disclose the composition of beta-secretase, or said beta-secretase with an inhibitor affinity is at least 1/100 of that exhibited toward SEQ ID NO:43, wherein the composition is crystalline form.

It would have been obvious to one having ordinary skill in the art at the time of invention to have the composition of beta secretase taught by Gurney et al. and modify it by crystallization of the enzyme.

The motivation that is obvious to one having ordinary skill in the art is to have the composition that is in more stable form than dissolved protein and the composition that enables crystallographic studies of interaction between the enzyme and its inhibitor with

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the purpose of improving the inhibitor properties. Additional motivation is provided by Powell et al. who write in column 19, line 28: "This invention provides methods of treating abnormal conditions...related both an excess and insufficient amounts of ASP2 polypeptide activity [beta-secretase of SEQ ID NO:2 of the instant invention wherein residue in position 130 is different than valine]. If the activity of ASP2 polypeptide is in excess, several approaches are possible." In line 46 of column 19, Powell et al. write, "In another approach, soluble forms of ASP2 polypeptides still capable of binding the ligand in competition with endogenous ASP2 polypeptide may be administered." Crystalline solution of the beta-secretase is more stable than soluble form of that protein and when administered to a subject in need is converted in the body into a soluble form.

The probability of success in obtaining the claimed invention is 100%, because the methods of protein crystallization are routinely used in the art.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made, and was, as a whole, *prima facie* obvious.

1.3. Double patenting rejection

All provisional obviousness-type double patenting rejections of claims 1-4, 15, 18, 22-25, 29-34 and 36 over the claims of US patent application No. 09/724,569 ('569) is maintained because Applicants did not file a terminal disclaimer. The non-provisional obviousness-type double patenting rejections of claims 1 and 2 over claims 1, 2, and 6 of US Patent No. 5,744,346, made in the Final Office Action of Feb. 20, 2004 are maintained, because Applicants did not file a the terminal disclaimer.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka whose telephone number is (571) 272-0944. The examiner can normally be reached on Monday-Friday from 10:00 a.m. to 4:30 p.m.

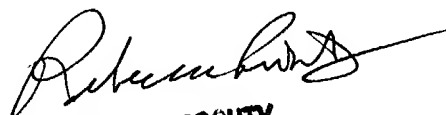
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Malgorzata A. Walicka, Ph.D.

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Patent Examiner


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